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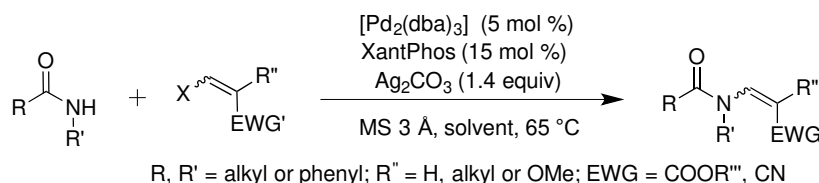
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Synthesis of Tertiary Enamides by Ag₂CO₃-promoted Pd-Catalyzed Alkenylation of Acyclic Secondary Amides.

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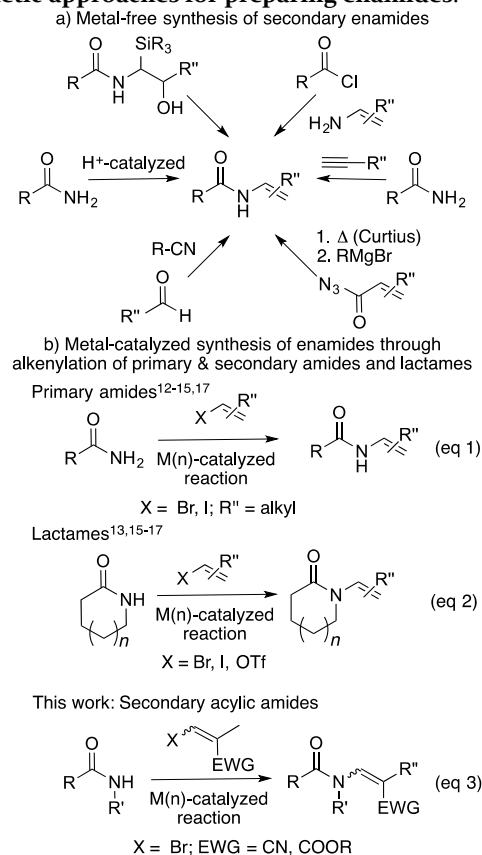


ABSTRACT: A Pd-catalyzed methodology for the preparation of tertiary enamides from acyclic secondary amides and bromo acrylates under mild reaction conditions has been developed using [Pd₂(dba)₃], XantPhos and Ag₂CO₃ as a base. The reaction occurs through a stereospecific metal-mediated oxidative-insertion mechanism.

In the last decade, metal-catalyzed C(sp²)-N and C(sp)-N bond-forming reactions with amines and amides have been under great development.¹ In particular, the elaboration of novel alkenylation reactions affording enamides² has attracted a lot of attention, as these functional groups are fundamental components of a large variety of natural products³ and versatile precursors of β-amino acids, the latter being important building blocks for preparing biologically active peptides, small-molecule pharmaceuticals and chiral synthons.⁴ With respect to metal-free protocols (e.g. acid-catalyzed condensation of amides and aldehydes,⁵ acylation of imines,⁶ Curtius rearrangement of α,β-unsaturated acyl azides,⁷ addition of amides to alkynes,⁸ condensation of aldehydes or ketones with nitriles,^{4f} elimination of β-hydroxy-α-silyl amides,⁹ and electroorganic synthesis,¹⁰ Scheme 1a), metal-catalyzed alkylation reactions have provided access to substituted enamides in high yields with a full stereocontrol on the double bond (Scheme 1b).¹¹ Among the recently described methods, Pd- and Cu-catalyzed coupling of alkenyl halides with amides are certainly very efficient. Following the first report by *Ogawa* and *Suzuki*¹² describing the stereospecific synthesis of enamides and enimides from vinyl bromides and potassium amides in the presence of a stoichiometric amount of CuI, the groups of *Buckwald*,¹³ *Porco*,¹⁴ and *Ma*¹⁵ have developed efficient Cu(I)-catalyzed variants that dramatically increase the scope and the chemical compatibility of these coupling reactions (Scheme 1b, eq 1) also starting from lactames (Scheme 1b, eq 2). Following the first protocols by *Mori* and *Kozawa* describing intramolecular Pd-catalyzed vinylation of β-lactams,¹⁶ versatile Pd-catalyzed variants have been also developed by *Wallace* and co-workers,^{17a} and later by *Willis*,^{17b} who reported the synthesis of tertiary enamides (Scheme 1b, eq

2) through a coupling reaction between an enol triflate and amides, carbamates or sulfonamides.

Scheme 1. Metal-free (a) and metal-catalyzed (b) synthetic approaches for preparing enamides.



Apart from the alkylation of secondary enamides, methods for directly accessing to tertiary enamides through direct alkenylation of acyclic amides under mild conditions are deficient (Scheme 1b, eq 3).¹⁹ This limits the versatility of tertiary enamides as valuable stable variants of enamines to be employed in the synthesis of natural products and heterocyclic compounds of biological relevance.^{18,19} Here, we thus describe the synthesis of tertiary *N*-alkyl and *N*-arylenamides through metal-catalyzed alkenylation reaction between acyclic secondary amides and β -halo acrylates and β -halo acrylonitriles (Scheme 1b-ii). As a matter of fact, this method is an effective strategy for synthesizing tri-substituted vinylogous imides and vinylogous *N*-acyl amino-nitriles.

Thus, our studies commenced by examining the general Cu(I)-catalyzed method¹⁴ (i.e. CuI (5 mol %), DMEDA (20 mol %), K₂CO₃, toluene, 110 °C) between *N*-methyl propionamide and (*E*)-3-bromo-methylacrylate. Unfortunately, under these reaction conditions, only starting materials were observed. The use of different ligands (1,10-phenanthroline, *N,N*-dimethylglycine), changing the solvent, temperature or base did not lead to any improvements. Therefore our attention was turned towards Pd-catalyzed methodologies. Taking into consideration the Pd-catalyzed reaction conditions used for the coupling of β -lactams to vinyl halides,¹⁶ (i.e. Pd(OAc)₂ (10 mol %), DPEphos (15 mol %), K₂CO₃, toluene, 110 °C), and applying them to the substrates of our interest, only degradation of the starting material was observed. The same observation was noted when XantPhos was used.

Table 1. Optimization of the Pd-catalyzed cross-coupling reaction between *N*-Methyl propionamide and (*E*)-3-Bromo-methylacrylate.^a

entry	catalyst	base	yield (%) ^{b,c}
1	[Pd ₂ (dba) ₃]	Cs ₂ CO ₃	64
2	[Pd ₂ (dba) ₃]	K ₂ CO ₃	15
3	[Pd ₂ (dba) ₃]	Na ₂ CO ₃	0
4	[Pd ₂ (dba) ₃]	Ag ₂ CO ₃	83
5	[PdCl(C ₃ H ₅) ₂]	Ag ₂ CO ₃	81
6 ^d	[Pd ₂ (dba) ₃]	Ag ₂ CO ₃	85
7	-	Ag ₂ CO ₃	0
8	[Pd ₂ (dba) ₃]	-	0

^aReaction conditions: *N*-methyl propionamide (0.3 mmol), (*E*)-3-bromo-methylacrylate (0.25 mmol), catalyst (5 mol %), ligand (15 mol %), base (0.35 mmol), MS 3 Å, THF. ^bAll yields refer to the isolated compound (SI). ^cAll gave full conversion. ^dMicrowave irradiation, 100 °C, 2 h.

On the other hand, after changing the catalyst precursor to [Pd₂(dba)₃] in the presence of XantPhos and Cs₂CO₃ under dry conditions at 65 °C for 16 h, 100% conversion was observed, affording after purification desired enamide (*E*)-1 in 64% yield (Table 1, entry 1). The use of weaker bases (K₂CO₃ and Na₂CO₃) resulted in reduced yield or no formation of enamide (*E*)-1 at all, respectively (Table 1,

entries 2-3). Instead, in the presence of Ag₂CO₃, an improvement of the yield to 83% was noted (Table 1, entry 4). From these results, one could presume a marked activation action of the Ag(I) ions on the halo methylacrylate. However, when the reaction was performed in the presence of AgBF₄ or AgOTf, no traces of the product were observed. This supports the idea for which a synergistic effect between the Ag(I) ions and the basic counterion improves the efficiency of the C-N coupling. Furthermore, when other Pd sources, such as [PdCl(C₃H₅)₂] (Table 1, entry 5), or microwave irradiation at 100 °C for 2 h, were used, yields higher than 80% were obtained. No formation of enamide (*E*)-1 was observed a) in the absence of either [Pd₂(dba)₃] or Ag₂CO₃ (Table 1, entries 7-8) or b) when the ligand was changed to Jackiephos,²⁰ notorious to be effective for the formation of sterically-demanding substrates. Examination of a variety of other ligands, including DPEphos and Xphos, proved to be also ineffective. Changing the solvent, from THF to toluene or 1,4-dioxane had only a minor effect in the outcome of the reaction and hence THF was used. The conditions disclosed in Table 1 entry 4 on the (*E*)-3-bromo-methylacrylate have been successfully extended to its (*Z*)-stereoisomer, stereospecifically producing related (*Z*)-enamide **2** by retention of the configuration at the substituted vinylic carbon (Table 2, entry 3). This was further confirmed with δ -valerolactam, for which the reaction with (*Z*)-3-bromo-methylacrylate also yielded molecule **3** as the (*Z*)-isomer (Scheme 2).

Table 2. Effect of the halide on the cross-coupling reaction using and (*Z*)-3-halo-ethylacrylate.

X	conversion (%)	yield (%)
F	0	0
Cl	100	62
Br	100	70
I	100	79

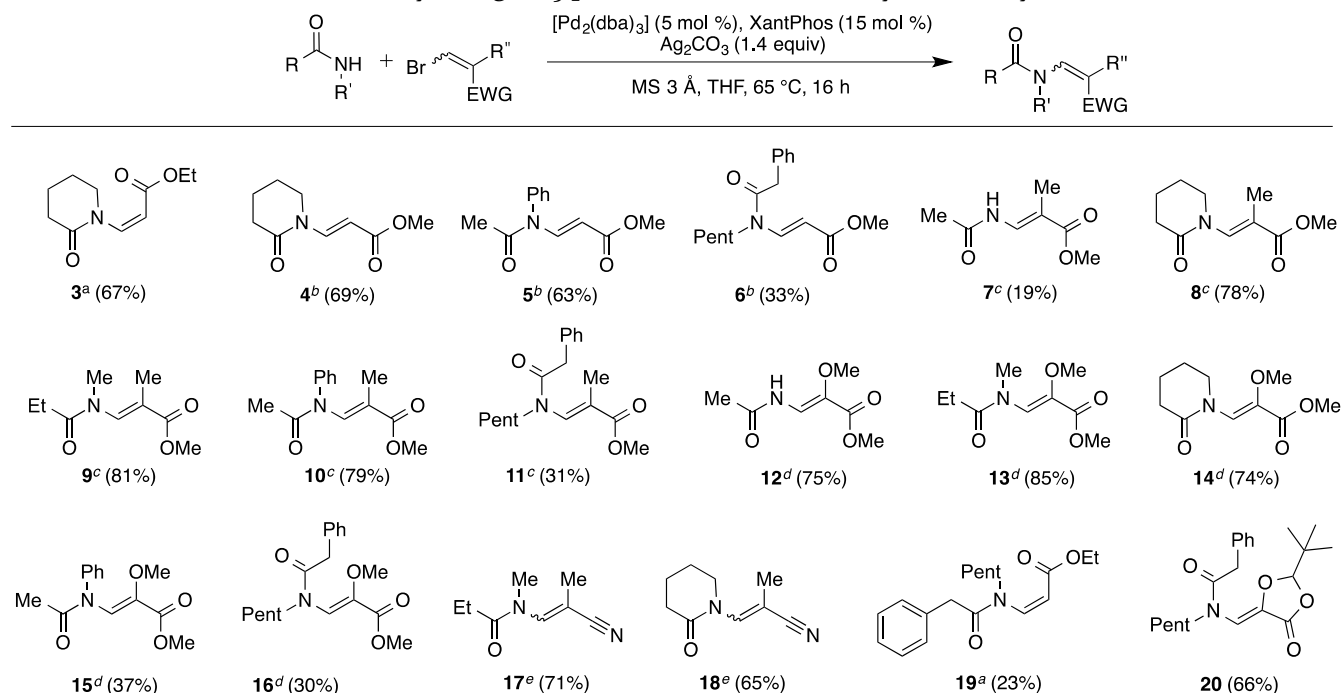
When the acryl bromide was switched to the chloro and iodo analogues (Table 2), enamide (*Z*)-2 was formed in 62% and 79% yield respectively. In contrast, the fluoro precursor gave no sign of desired enamide (*Z*)-2. Take together, these results promoted us to exclude an addition-elimination mechanism and are fully consistent with a metal-mediated oxidative-insertion mechanism. Having in hand the optimized reaction conditions and the fundamental mechanistic insights, the attention was then focused in examining the generality of this method, by varying both the vinyl and the amide substrates.

As outlined in Scheme 2 (the *E* and *Z* notations are omitted for clarity reasons), a variety of tertiary *N*-alkyl and *N*-aryl enamides have been prepared employing the Ag₂CO₃-promoted Pd-catalyzed conditions from moderate to good yields. *N*-Methyl, -phenyl and -pentyl substituted amides were all successfully coupled to acrylic bromides, and the obtained yield confirmed the steric trend, with the *N*-pentyl substrate being the less reactive. For example, when (*E*)-3-bromo-methylacrylate was reacted with the relevant amide,

enamides **5** and **6** were obtained in 83%, 63% and 33% yield, respectively. In general, when the *N*-pentyl-based amide is coupled with any acyclic acrylic substrate, tertiary enamides with modest yields at around 30% were obtained (enamides **6**, **11**, **16** and **17**). As observed for (*E*)-**1** and (*Z*)-**2**, the geometry of the double bond in the acryl halides has a modest effect on the yield. In particular when (*Z*)-3-bromo-ethylacrylate was used instead of (*E*)-3-bromo-methylacrylate, the *E* isomer of the relevant enamide was obtained vs the *Z* isomer in the second case, with only slightly higher yield ((*E*)-**1** 83% vs (*Z*)-**2** 70%). This is further confirmed when comparing the outcome of the reaction leading to the formation of

enamides **3** vs **4** and **6** vs **19**. Notably, the protocol is also effective for the electronically-rich acrylic derivatives, such as 3-methyl and 3-methoxy substrates, which gave rise to enamides **8-11** and **12-16**, respectively. It is worth pointing out that, these reaction conditions are certainly compatible with the majority of thermally unstable and volatile vinyl bromides. The method could be extended to functional substrates as 5-(bromo-methylene)-1,3-dioxolan-4-one (molecule **22**, see SI for its synthesis), a potential precursor for preparing β -amino α -ketoacids. When the 1,3-dioxolan-4-one was reacted with *N*-pentyl amide, enamide **20** was isolated in 66% yield.

Scheme 2. Pd-catalyzed Ag₂CO₃-promoted formation of acyclic tertiary enamides.



Starting from ^a*cis*-3-bromo-ethylacrylate. ^b*trans*-3-bromo-methylacrylate. ^cmethyl-(*E*)-3-bromo-methylacrylate. ^dmethyl-(*Z*)-3-bromo-2-methoxyacrylate. ^e1:1 mixture of *cis*- and *trans*-3-bromo-2-methylacrylonitrile. All yields refer to the isolated and purified compounds.

Attempting to elucidate the double bond configuration of one of the tertiary enamides bearing a trisubstituted vinyl group, two types of crystals (rod- and rhombic-like) deriving from the crystallization of product **20** (being the only solid derivative) were obtained and analyzed by single X-ray diffraction (Figure 1). The first proved to be the *Z* isomer of enamide **20** ((*Z*)-**20**, Scheme 3) and, to our surprise, the second crystals resulted from dispiro derivative **21** featuring a central cyclobutane ring (Figure 1). Notably, no crystals of isomer (*E*)-**20** were found. Re-dissolution of the crystals in non-acidic CDCl_3 gave the same ^1H -NMR spectrum as that obtained before crystallization, namely that of **20** with no sign of the typical proton resonances of the cyclobutyl ring, suggesting that the dispiro derivative perishes in solution and can be isolated only at the solid state. Complementary variable temperature (VT) ^1H -NMR investigations of a CDCl_3 solution containing **20** show coalescence between 5 and -10 °C of the proton resonances in the diagnostic enamidic chemical shift region, suggesting the presence of a dynamic equilibrium (see SI, Figure 5). Unfortunately, the overlap with the

aromatic proton resonances hampers the univocal assignment of the coalescing peaks (see SI, Figure 5). However, when similar VT investigations were performed with enamide **9** (see also **13**, SI Figures 1 and 6), the ^1H -NMR spectrum at rt displayed a vinylic proton resonance at 7.27 ppm that, upon cooling to -40 °C, shifts and clearly splits into two peaks centered at 7.19 and 6.72 ppm, respectively. Likely, these peaks correspond to the vinylic proton resonances of isomers (*E*)-**20** and (*Z*)-**20**. In contrast, the VT ^1H -NMR spectra of all enamides bearing doubly-substituted acryl (*e.g.*, **4**, (*E*)-**1** or (*Z*)-**2**, Figure SI.7) and of the Br-derived acrylate precursors (see SI, Figures 3-4) displayed no coalescence of the vinylic proton resonances. These observations promoted us to hypothesize that the enamides bearing acryl moieties decorated with EDGs (Me or OMe) undergo *E/Z* isomerization in solution, and therefore the products are obtained as isomeric mixtures at rt. Likely, this could hypothetically occur through the formation of a dispiro cyclobutane species that serve as intermediate of a fast dynamic equilibrium possibly involving sequential ring-opening and ring-closure

reactions (Scheme 3). On the contrary, all enamides bearing a vinyl moiety substituted with only EWGs are thermally stable at rt and can be stereospecifically prepared by this procedure.

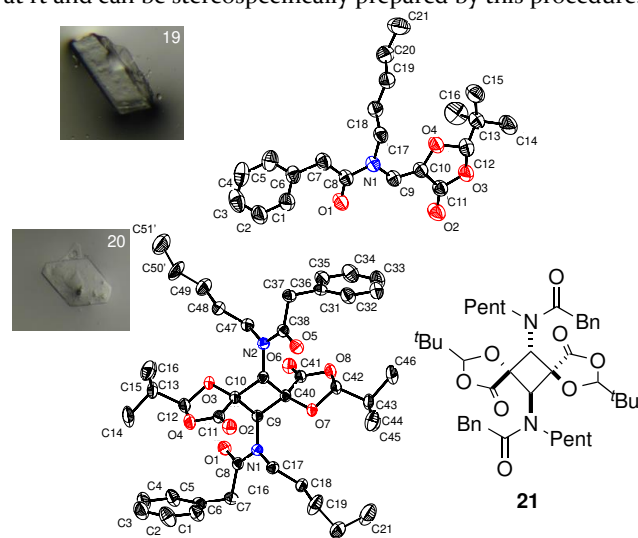
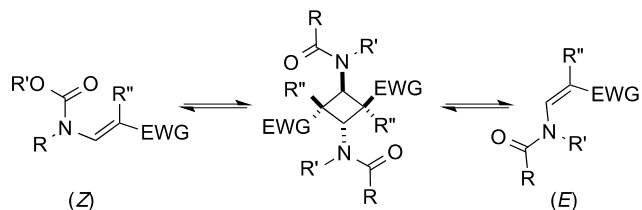


Figure 1. ORTEP representation of (*E*)-**20** and cyclobutyl derivative **21** as determined by X-ray analysis (space group: *P*2₁/*c*). Atomic displacement parameters, obtained at 223K, are drawn at the 30% probability level.

Scheme 3. Proposed *E/Z* isomerization in solution mediated by a dispiro cyclobutane intermediate.



In conclusion, we have demonstrated an Ag_2CO_3 -promoted Pd-catalyzed alkenylation procedure providing access to acyclic tertiary enamides starting from acryl bromides and sterically-encumbered *N*-substituted amides. A wide range of enamides was synthesized, proving the versatility of the method. The reaction likely undergoes through a stereospecific oxidative-insertion mechanism favored by the presence of Ag_2CO_3 . VT ^1H -NMR experiments showed that the enamides bearing acryl moieties decorated with EDGs undergo *E/Z* isomerization in solution. The ease of access towards tri-substituted vinylogous imides and *N*-acyl amino-nitriles,²¹ makes this Pd-catalyzed alkenylation method appealing to organic chemists.

ASSOCIATED CONTENT

Supporting Information

Synthetic protocols and spectroscopic data, relevant X-ray data for molecules (*E*)-**20** and **21**, VT ^1H -NMR spectra of all enamides. The Supporting Information is available free of charge at <http://pubs.acs.org>.

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